## REMARKS

The specification has been amended at page 22 to insert sequence identifiers as required by the Examiner. A new sequence listing (in paper and computer readable forms) has also been submitted to replace the previous sequence listing.

In the amendments herein, claim 4 has been amended. Support for this amendment can be found throughout the specification as filed, e.g., at the paragraph bridging pages 28-29. Now pending in the application is claim 4.

No new matter has been added by these amendments.

The amendment and/or cancellation of claims is without prejudice or disclaimer of the subject matter thereof and was done solely to expedite prosecution of the present application. Applicants reserve the right to pursue the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

Priority Claim and Request for Corrected Filing Receipt

The present application is the U.S. national stage application under 35 USC §371 of PCT/JP03/00089, as correctly noted in the Official Filing Receipt dated 01/26/2006. However, Applicants note that the records of the Patent Office do not appear to reflect that the present application claims priority under 35 USC §119 to Japanese application JP2002-005326, filed January 11, 2002. Applicants note that: the PCT application as published indicates this priority claim; the Form PCT/IB/304 issued in connection with the PCT application indicates this priority claim and the receipt of the priority document (a copy of Form PCT/IB/304 was filed with the instant U.S. application filing papers); the original "Declaration and Power of Attorney" signed by the inventors (and filed with the instant U.S. application filing papers) in the present application indicates this priority claim; and that the certified copy of the priority application has been received by the U.S. Patent Office (as shown in PAIR). It is believed that all requirements for establishing entitlement to the priority claim have been met.

Applicants therefore request that a corrected filing receipt be issued reflecting this foreign priority claim, and that all Patent Office records be updated appropriately.

Sequence Compliance

In the Office Action, the Examiner required the identification of certain sequences shown in Figure 3. The specification has been amended to insert the required identifiers, and a new sequence listing in compliance with 37 CFR 1.821 et seq. is submitted for entry herewith. Support for the amendments in the new sequence listing is found in Figs. 3(a) and 3(b). No new matter has been added.

Applicants respectfully contend that the application is sequence compliant.

Objection to the Drawings

In the Office Action, the Examiner objected to the drawings as containing sequences not identified by SEQ ID NO. In response, Applicants have amended the description of the drawings, as discussed above, to identify the sequences in Figures 3(a) and 3(b).

Applicants respectfully contend that the objection has been overcome and should be withdrawn, and such action is requested.

Rejection under 35 U.S.C. §112, first paragraph (enablement)

Claim 4 stands rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is traversed.

Claim 4 (as now pending) is directed to method of evaluating onset or onset possibility of rheumatoid arthritis in a human subject, the method comprising the comprising the steps of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject; wherein

the step of evaluating comprises determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject.

The Office Action discusses the Wands factors and states that claim 4 lacks enablement. Applicants do not agree with this analysis; some points are discussed in more detail below.

In the discussion of the Wands factors, the Office Action states that "the claims broadly encompass the absence of nt805 HOMO being predictive of the possibility of RA . . . it appears that the absence of detecting a gene that encodes SEQ ID NO1 is not predictably associated with the onset or possibility of onset of RA." This statement is traversed.

As discussed previously and as shown in Figure 4 of the application, both in RA families and Sporadic families, the presence of the "nt805 homo" (homozygous 3-base-insertion mutation) genotype is associated with the development of RA. Indeed, the Examiner stated (in the Office Action dated April 27, 2007) that "it appears that an association exists for humans homozygous for the presence of 'GGT' at position 805-807" (Office Action dated April 27, 2007, at page 5). Moreover, Applicants provided additional data regarding this association in the "Declaration Under 37 CFR 1.132" (the "Declaration") filed September 11, 2007, demonstrating a statistically significant trend in that study group, as determined by the $x^2$ test.

In view of the data presented in the subject specification, and in the Declaration, Applicants contend that one of ordinary skill in the art would be able to evaluate the onset or onset possibility of rheumatoid arthritis in a human subject by detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject; and evaluating the onset or onset possibility of rheumatoid arthritis in the subject; wherein the step of evaluating comprises determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject, as presently claimed.

The Office Action further discusses references (Hirschhorn et al. and Ioannides) that suggest that association studies are not reproducible. Applicants respectfully

contend that no reason has been advanced to suggest that the studies presented in the present application and the Declaration are unreliable.

Still further, the Office Action states (at page 8) that "the [present] claim merely requires the presence of SEQ ID NO 1". The Office Action also states that "the claims does not require a step of correlating the presence or absence of SEQ ID NO 1 with RA." These statements are traversed.

Applicants point out that pending claim 4 recites the steps of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject, and determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject. Thus, the present claim does not "merely require[] the presence of SEQ ID NO 1"; moreover, the claim additionally provides that the homozygous presence of the gene indicates an increased onset possibility of rheumatoid arthritis.

In the section titled "Response to Arguments", the Office Action states that the data provided in the specification and in the Declaration are from two different populations and "leads one to question what the two populations are and if the results are predictable across all populations." Applicants respectfully submit that the data confirm that the homozygous presence of a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is associated with the development of RA. While the group studied as described in the Declaration is a group that includes many subjects having the homozygous 3-base-insertion mutation, as described above and in previous Responses, in both the study group discussed in the specification and in the study group discussed in the Declaration, the homozygous presence of the gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is associated with the tendency to develop RA. Applicants respectfully contend that any differences in the study populations do not call into question, and in fact confirm, that the pending claim is enabled.

Applicants respectfully contend that the specification provides enablement for the full scope of the pending claim, and, furthermore, that the claim meets all the

requirements of, *inter alia*, 35 USC §112. Reconsideration and withdrawal of the rejection is requested.

Rejection under 35 U.S.C. §112, second paragraph

Claim 4 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting "a gene homozygously coding". This rejection is traversed.

In the amendments presented herein, claim 4 has been amended to provide that the claimed method includes the step of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject. Thus, the objected-to language is no longer recited in claim 4.

In the Office Action, Claim 4 was also said to be indefinite because "it does not recite a step suggesting whether the homozygous presence or absence of SEQ ID No 1 results in an increased or decreased possibility of onset of RA." This statement is traversed. Without agreeing with the rejection, claim 4 has been amended to recite that the claimed step of evaluating comprises determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject.

Applicants submit that claim 4 is not indefinite and fully complies with all the requirements of 35 U.S.C. §112. Reconsideration and withdrawal of the rejection is proper and the same is requested.

Rejection under 35 U.S.C. §102

Claim 4 stands rejected under 35 U.S.C. §102(a) and §102(e) as allegedly anticipated by Hillman et al., U.S. Patent Publication No. 2002/0123054 (hereinafter, "the Hillman application"). This rejection is traversed.

The Office Action states that the Hillman application discloses "a method of comprising the step of detecting the presence or absence of SEQ ID NO 1 and the step of evaluating the onset of RA". Applicants do not agree. It is Applicants' understanding that the Hillman application does not disclose a gene sequence encoding the (mutant)

angiopoietin of SEQ ID NO.:1, but rather discloses only the detection of the wild-type angiopoietin-1 gene. Thus, contrary to the statement in the Office Action, the Hillman publication does not disclose a step of detecting the presence or absence of SEQ ID NO.:1.

In addition, Applicants point out that claim 4 as pending requires the step of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject, and also recites that an evaluating step includes determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject. The Hillman application does not teach or suggest detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject, and does not teach or suggest an evaluation step includes determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject. Therefore, the Hillman application does not teach or suggest the presently-claimed method and cannot anticipate the pending claim.

Claim 4 stands rejected under 35 U.S.C. §102(a) as allegedly anticipated by a publication of Shiozawa et al, Nippon Rinsho (2002) (hereinafter, "the Shiozawa publication"). This rejection is traversed.

As an initial matter, Applicants note that the Shiozawa publication is, in pertinent part, the work of the present inventors published less than one year before the PCT filing date of the present application, and therefore is not available as prior art under 35 U.S.C. §102(a). Moreover, the present application claims the benefit of priority to application JP2002-005326, filed January 11, 2002 (prior to the publication date of the Shiozawa publication) (see above).

Still further, the Shiozawa publication does not disclose a method of detecting whether a gene coding a protein comprising the amino acid sequence of SEQ. ID NO.:1 is present homozygously in the subject, and does not teach or suggest an evaluation step includes determining that the onset possibility of rheumatoid arthritis is increased if the gene is present homozygously in the subject. Therefore, the Shiozawa publication

does not teach or suggest the presently-claimed method and cannot anticipate the pending claim.

Reconsideration and withdrawal of the rejections is proper and the same is requested.

**CONCLUSION**

For at least the above reasons, Applicants contend that the application is in condition for allowance. Early and favorable consideration of the application is earnestly solicited.

Applicants request any extension of time necessary for this response to be considered timely filed. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Reference No. 61646 (70904), Customer No. 21874.

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Respectfully submitted,

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